Restriction Requirement

Applicants hereby confirm the provisional election made with traverse by Mr. J.D. Evans during a telephone conversation with the Examiner on August 5, 2002.

Applicants traverse the restriction requirement because the Office Action simply equated scientific differences, sometimes even minute differences in the claimed elements (e.g. different antiviral agents such as AZT and 3TC *in addition to* bpV) with the legal concept of "independent and distinct" inventions, as required under 35 U.S.C. §121. In fact, for two claims to be properly restricted, they must be (1) independent and distinct, *and* (2) pose a *serious* burden on the Examiner. See MPEP §803. Applicants respectfully submit that the Office Action, in making this additional round of restriction requirements, has not established that the claims in the various alleged groups are independent, or distinct from each other. Accordingly, applicants respectfully submit that the restriction requirements are improper and all claims should be examined on the merit.

Drawings

Applicants hereby submit formal drawings which are believed to overcome all objections by the draftsperson. Applicants submit that the formal drawings

only remedy informalities contained in the drawings previous of record and do not add any new matter.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-3, 5-10 and 16-19 remain rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. For the reasons detailed below, applicants respectfully traverse and request that the rejection be withdrawn.

The first reason, presented in the Office Action for the assertion that the claims directed to treating viral infections using peroxivanadium lack enablement, is that the data presented in the present disclosure are alleged to be "in direct conflict" with the prior art, specifically Barbeau *et al.*, 1997 (Journal of Biological Chemistry 272:12968-12977). As detailed below, however, a closer examination of the data will show that the data in Barbeau *et al.* are *not* in conflict with the data in the present invention.

Figures 8 and 9 of Barbeau *et al.* showed that following bpV treatment the reverse transcriptase activity of HIV-1 in a T-cell line latently infected with the virus is increased. From this observation the authors concluded that pV compounds stimulated HIV-1 replication in latently infected T cells. There is no indication whatsoever that there was an increase in "viral particle release" (as asserted in the third-to-last line on page 10 of the Office Action). The cell lines used in Barbeau *et al.* were the J1.1 and U1 cell lines, which are latently infected with HIV, i.e. the virus is integrated within the cell chromosome.

In comparison, the cell lines and primary cells used in the present invention were not latently infected with HIV prior to bpV treatment, and different viral encoded proteins were measured as indicators of anti-infection activity of bpV. For example, Figure 1 shows that the viral envelope protein p24 is dramatically decreased, and various other figures show that virus-encoded luciferase activity was decreased as a result of bpV treatment.

Even assume the results in Barbeau *et al.* is valid and repeatable, they are nonetheless consistent with the observations in the present disclosure. Although not wishing to be bound by theories or speculative discussion of possible mechanisms of the invention, applicants submit that several possibilities exist. The data in Barbeau *et al.* probably indicate that the LTR promoter is activated by bpV, leading to increased proviral transcription and replication including expression of some "early genes" of the virus. Data in the present invention indicate that "late gene" expression is inhibited by bpV. Thus, although viral genomic replication may be increased, if certain critical viral proteins are not expressed, the infection cycle is disrupted, and detrimental effects by the presence of the virus in cells are decreased, resulting in effective treatment. Another likelihood is that bpV treatment may inhibit HIV infection prior to viral integration, resulting in less cells being infected, and leading to a reduction in viral production. This scenario is consistent with the general knowledge that HIV viral genes are not efficiently expressed from non-integrated proviral DNA (see *e.g.* Wisckerchen and Muesing, 1995, J. Virol. 69-376-386, copy of abstract attached as Exhibit I).

Drugs that are effective only at a particular stage of the viral infection cycle are common in the art. For example, an effective HIV entry blocker, such as the T20 molecule (Trimeris Inc.), are ineffective in preventing the release of infectious virus from latently infected cells. If one were to measure the release of infectious virions from latently infected cells, one would prematurely conclude that T20 is a drug with no potential therapeutic potential.

In other words, regardless how bpV affects HIV viral enzyme activities, it possesses overall anti-viral activities at the level of viral expression and can reduce the pathological impact of the virus on cells. As evidence of such activity, applicants have conducted additional tests, showing that bpV treatment prevents the decline of CD4+ human T-cells as a consequence of HIV invention (see attached Exhibit II, which will be presented as a declaration by the present inventors if deemed necessary by the Examiner).

The second reason in the Office Action for the lack-of-enablement rejection is that the disclosure only contains *in vitro* and animal data, and because of the possibility that *in vitro* or animal models do not guarantee *in vivo* or clinical successes, the invention is not enabled. In this regard, applicants respectfully submit that an improper legal standard was used in the Office Action.

Many drugs that have shown efficacy in *in vitro* or *in vivo* animal models indeed do not reach commercialization and never end up on the pharmacy shelves. However, this does not invalidate in any way the usefulness of such models. It is well established law that therapeutic utility sufficient under the patent law is not to be confused with the requirements of the FDA with regard to

safety and efficacy of drugs to be marketed in the United States. See e.g. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). To this end, the statements cited in the Office Action from popular press regarding clinical efficacy and the ratio of drugs under experimental investigation that successfully reach market are irrelevant to the enablement analysis under 35 U.S.C. § 112, ¶ 1. The proper issue to address is whether the *in vitro* data "correlate" with claimed method of treatment claims.

According to §2164.02 of the MPEP

> [a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes working examples if that example correlates with a disclosed or claimed method invention. . . [I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

Furthermore, a rigorous or an invariable exact correlation is not required, and a reasonable correlation is sufficient (citing, *inter alia*, *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)).

In vitro and animal experimentation represent the first in a long series of steps needed before a drug makes it way to the market. In many instances, the failure to reach commercialization is attributable to several other factors, such as high toxicity, low bioavailability, short half-life and high manufacturing cost.

The Office Action cites one paper (Mitsuya et al., Science 226 : 172-174, 1984) on the *in vitro* anti-HIV effectiveness of suramin that did not correlate with clinical success, but it is well known that the failure of suramin in clinical application is due to its high toxicity. Even the paper itself cautioned the readers on the significant toxicities associated with suramin and that the use in humans should be monitored very closely. Sandström *et al.* (Lancet, vol 1 pp 1480-82) similarly demonstrates that suramin is toxic, but is nonetheless effective. There is no indication in either Mitsuya *et al.* or Sandström *et al.* that "the use of *in vivo* tests is not accepted as *in vivo* activity."

The models used in the present application are widely used and accepted by those in the relevant art to test HIV treatment methods and compositions. The Office Action presented no specific evidence that the *in vitro* data do not correlate with the claimed *in vivo* methods. Furthermore, as discussed above, further data (see Exhibit II) validate that the *in vitro* data correlates with *in vivo* therapeutic results, thus proving that the claimed methods are enabled.

In summary, when applying the proper legal standard, and when weighing all evidence as a whole, one skilled in the art would accept that the *in vitro* models used in the present specification correlate with the claimed treatment methods, and the claims are enabled.

Applicants respectfully submit that all claims are now in condition for allowance, and earnestly solicit an early indication to that effect. In the event that there are any questions concerning this amendment or the application in

general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #2097/49123).

Respectfully submitted,

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